PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
George Barrie Kitto and
Mary Susan Burnett

Serial No.: 09/244, 195

Filed: February 4, 1999

For: LIVE VACCINE FOR HUMAN IMMUNODEFICIENCY VIRUS

Group Art Unit: 1648

Examiner: Jeffrey S. Parkin

Atty. Dkt. No.: D6073/CLFR:167US

CERTIFICATE OF MAILING
37 C.F.R. §1.8

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March 9, 2006
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David L. Parker

REPLY BRIEF

Sir:

Appellants hereby submit this Reply Brief in accordance with 37 C.F.R. §41.41, in response to the Examiner's Answer dated January 11, 2006, making the due date March 11, 2006. A Request for Oral Hearing is attached along with the required fee. It is believed no other fees are required, however, if we are mistaken, the Commissioner is authorized to withdraw any such fees from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/CLFR:167US.

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There are currently two obviousness rejections pending, to which Appellants now provide their reply to the Examiner's Answer.

Rejection of All Claims as Obvious over Brey et al. ("Brey") in view of Georgiou et al. ("Georgiou") and Thimmig et al. ("Thimmig")

Brey is the principal reference relied upon by the Examiner. The Answer erroneously characterizes Brey as concerning the general topic of "the preparation of attenuated bacterial ... expression systems ... that are useful for the expression of heterologous (*e.g.*, malaria) antigens." Answer at p. 5. This is an incorrect statement clearly not supported by substantial evidence – Brey is specifically limited to malaria and says nothing about "heterologous antigens." Appellants have been unable to identify any teaching in Brey regarding the "expression of heterologous antigens," and the Answer fails to direct us to any such teaching. Further, to suggest that Brey teaches "malaria" antigens as a mere example of a "heterologous antigen" is again, simply incorrect. From Appellants' reading, Brey teaches and suggest ***only*** malarial antigens:

> The present invention is directed to attenuated strains of enteroinvasive bacteria that express peptides and proteins related to epitopes of the malaria parasites of the genus Plasmodium. The bacterial strains of the present invention which can multiply in a host without causing significant disease or disorder, and which express Plasmodium-related peptides that induce a protective immune

> response against malaria, can be used in live vaccine formulations for malaria. Such vaccine formulations can be univalent or multivalent.... Col. 1, lines 6-16. ...
>
> The present invention is directed to attenuated strains of enteroinvasive bacteria that express peptides and proteins related to epitopes of the malaria parasites of the genus Plasmodium. The bacterial strains of the invention which can multiply in a host without causing significant disease or disorder, and which express Plasmodium-related peptides that induce a protective immune response against malaria, can be used in live vaccine formulations for malaria. Such vaccine formulations can be univalent or multivalent. ... Col. 6, line 64 – Col. 7, line 5 ...
>
> The present invention is directed to attenuated strains of enteroinvasive bacteria that express peptides and proteins related to epitopes of the malaria parasites of the genus Plasmodium. The bacterial strains of the present invention which can multiply in a host without causing significant disease or disorder, and which express Plasmodium-related peptides that induce a protective immune response against malaria, can be used in live vaccine formulations for malaria. Such vaccine formulations can be univalent or multivalent. ... Col. 11, lines 7-16.

Since Brey is clearly limited in its scope to the treatment of the parasitic disease, malaria, there in no basis in Brey for applying such an approach to raise an immune response against viral antigens, and the Answer points us to none. As noted by the Court of Appeals for the Federal Circuit, "[a] person of ordinary skill in the art is also presumed to be ***one who thinks along the lines of conventional wisdom in the art and is not one who undertakes to innovate***, whether by patient, and often expensive, systematic research or by extraordinary insight; it makes no difference which." *The Standard Oil Company v. American Cyanamid Co.*, 227 U.S.P.Q. 293 (Fed. Cir. 1985) (emphasis supplied). Thus, it is evident from *Standard Oil* that one of skill in the art, faced with Brey, would in no way be motivated by Brey to apply its teachings to a totally unrelated problem – such a person would only be motivated by Brey with respect to malarial therapies, not that of the totally unrelated HIV using a transactivating protein ("*tat*") or an HIV reverse transcriptase ("*rev*") antigen.

Turning now to the Georgiou reference, Appellants have searched this referenced and can find only one excerpt in any way relating to HIV:

> Prototype live bacterial vaccines have been prepared using cells having sequences from the influenza virus, cholera toxin B subunit and the gp 120 glycoprotein of HIV-1 expressed on their surface. However, the presence of a fragment of a protein from an infectious agent often does not give satisfactory protection against disease (Dougan et al. 1989).

Georgiou, col. 13, lines 28-35. This excerpt from Georgiou, the sole excerpt that we can find relating to HIV, is notable for two reasons. One, it mentions only the gp 120 glycoprotein antigen of HIV in passing, and says nothing about other HIV antigens. More notably, though, the passage indicates that such prior attempts were ***failures***. Clearly there is no basis in Georgiou, alone or in combination with Brey, for maintaining a prima facie obviousness rejection of the present claims, directed to eliciting an immune response against the HIV tat or rev gene products.

Thimmig does not cure the foregoing deficiencies in the rejection. Thimmig appears to simply relate to the cloning and expression of the HIV *rev* gene. However, we can find no disclosure here that teaches or suggest that the *rev* gene would be an appropriate or useful vaccine candidate, alone or in the context of a *Salmonella* expression host.

Accordingly, there is no substantial evidence basis on the current record to support a *prima facie* obviousness rejection over these three references. Brey concerns only malaria, and there is no expansive language to direct one of skill to apply its teachings to HIV, much less to the specific HIV *tat* or *rev* genes as herein claimed. Georgiou only mentions a *different* HIV gene in passing, and then only in the context of failure, and Thimmig appears to say nothing about using an HIV *rev* gene for eliciting an anti-HIV immune response – it does not even

appear to suggest that the *rev* gene product is immunogenic. In light of this, the Board is requested to overturn the Examiner.

Rejection of All Claims as Obvious over Hone et al. ("Hone") in view of Georgiou et al. ("Georgiou") and Thimmig et al. ("Thimmig")

Appellants now turn to the obviousness rejection of all the claims over Hone in view of Georgiou and Thimmig. Of course, the only difference here over the foregoing combination is the substitution of the Hone reference in place of the Brey reference. However, Appellants submit that this combination is similarly deficient, in that the Hone reference suffers from different, equally serious, inadequacies from an obviousness standpoint.

Hone is a research article that investigates the immunogenicity of various *Salmonella* constructs that incorporate the HIV gp120 gene. As discussed in the Abstract on page 203, the authors report a dramatic variability in the immunogenicity of such constructs, depending on precisely how the gp120 gene is inserted into the *Salmonella*. However, there are two additional points that arise out a consideration of the Hone reference that, we submit, dictates a conclusion of non-obviousness of the present invention:

First, it is important to bear in mind that the present claims are directed to eliciting both a humoral (*ie.*, antibody) response and a cellular (*e.g.*, CTL) response to the HIV tat or rev gene product. With that in mind, we note that Hone shows only an antibody response elicited in response to administration of the *Salmonella*/gp120 construct:

> The data presented here show that oral immunization of mice with *Salmonella* construct bearing cytoplasmic rgp120 induces a local humoral immune response against gp120. In contrast a *Salmonella* construct bearing periplasmic tgp120 induces both a local and systemic humoral response against gp120. ... paragraph bridging pages 205/206 [thus, in neither case, was a cellular immune response reported] ...

> Antigen-specific CD8+ CTLs were not detected after immunization with recombinant *Salmonella* vaccine vectors that expressed cytoplasmic influenza A nucleoprotein ... This latter study pointed to the possibility that antigen solubility and/or location might influence the induction of foreign antigen-specific CD8+ CTLs by *Salmonella*. ... In agreement, we found that cytoplasmic rgp120 forms inclusion bodies and does not induce detectable gp120-specific CD8+ CTLS in mice after oral or parenteral immunization. Collectively, these observations suggest that individual foreign antigen characteristics will dictate the *Salmonella* vector configuration that optimizes the level of such responses. It is reasonable to propose, therefore that *Salmonella* bearing surface-expressed gp120 will elicit gp120-specific CD8+ CTLs. Page 206, paragraph bridging columns 1 and 2.

Thus, the foregoing excerpt makes it clear that the authors never identified the successful generation of a cell-mediated response against gp120 using the Salmonella approach. Moreover, there was significant variation in the humoral response observed – in one approach not even a systemic humoral response was observed, much less a cellular response!

We would like, however, to highlight and address what are believed to be erroneous statements put forth by the Examiner in the Answer with regard to this rejection. First, the Examiner states that the broadest claims are "simply directed toward the generation of a cellular immune response." This is incorrect, as independent claim 6 clearly requires both a cellular and a humoral immune response. More importantly, though, the Answer goes on to suggest that a humoral response necessarily includes a T-helper response and is thus really both a humoral and a cellular response as required by the claims. This argument is unsupported by the claim language itself, which clearly denotes a ***separate*** humoral and cellular response, and conveniently overlooks the references admission, noted above, that no cellular response was obtained.[1]

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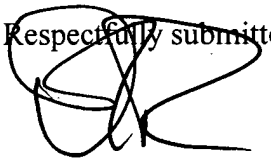
[1] The Examiner tries to argue that dependent claim 8 supports the conclusion that a T-helper response was intended as a type of cellular response. This is incorrect: claim 8 simply further defines the "immune response" of claim 1 as "comprising" a mucosal IgA response and a helper T cell response.

Lastly, and perhaps more importantly, there is simply no basis in Hone to suggest a substitution of the HIV tat or rev gene for the gp120 gene taught by Hone. Its teachings are clearly limited to gp120 and, as argued above with respect to the first rejection, there is simply no basis in the secondary references of Georgiou or Thimmig that would suggest a substitution of the *tat* or *rev* genes for gp120, or that such a substitution would be successful. Indeed, if anything, Hone indicates that that any substitutions would only introduce even more uncertainty. The mere fact that the Examiner has identified a reference that teaches the cloning and characterization of the HIV rev gene (but which says nothing about the antigenicity of such a protein or its use to elicit an immune response) in no way provides the necessary, missing motivation to substitute that *rev* gene for the gp120 of Hone.

It is respectfully submitted, in light of the above, none of the pending claims is properly rejected under 35 U.S.C. §103. Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,



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